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PRIORITY DOCUMENT

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607025179

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FEE RECORD SHEET

PTO-1556
(5/87)

Appendix A

PROVISIONAL APPLICATION COVER SHEET

60/025179

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(b)(2).

Docket Number P8009-6004		Type a plus sign (+) inside this box →	+

INVENTOR(S)/APPLICANT(S)

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TITLE OF THE INVENTION (280 characters max)

THERAPEUTIC FORMULATIONS CONTAINING VENOM OR VENOM ANTI-SERUM EITHER ALONE OR IN COMBINATION FOR THE THERAPEUTIC PROPHYLAXIS AND THERAPY OF NEOPLASMS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

- ☒ Specification — *Number of Pages* 45
- ☐ Drawing(s) — *Number of Sheets* ____
- ☐ Small Entity Statement
- ☐ Other (specify) ____

METHOD OF PAYMENT *(check one)*

☐ A check or money order is enclosed to cover the Provisional filing fees ☒ The Commissioner is hereby authorized to charge any underpayment or credit any overpayment to Deposit Account No. 14-1060	PROVISIONAL FILING FEE AMOUNT(S)	$150.00

The invention was made by an agency of the United States Government or under a contact with an agency of the United States Government.

- ☒ No
- ☐ Yes, the name of the U.S. Government agency and the Government contract number are: ____

Respectfully submitted,

SIGNATURE Kevin C. Brown Date: 9/11/96

TYPED or PRINTED NAME Kevin C. Brown REGISTRATION NO. 32,402

☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

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PATENT

TITLE: THERAPEUTIC FORMULATIONS CONTAINING VENOM OR VENOM ANTI-SERUM EITHER ALONE OR IN COMBINATION FOR THE THERAPEUTIC PROPHYLAXIS AND THERAPY OF NEOPLASMS

INVENTOR: ELIZABETH SHANAHAN-PRENDERGAST

ABSTRACT

The present invention comprises the method of treating a host organisms (man or animal) in need of a drug having direct or prophylactic anti-neoplastic activity comprising the administration of a therapeutically effective amount of venom anti-serum alone or in combination with a known Phospholipase C anti-serum or a Phospholipase C inhibitory compound. A vaccine containing in whole or in part snake or insect venom components and Phospholipase C enzyme components. This patent presents pharmaceutical formulations containing snake and/or insect venoms, or extracts from such venoms which contain, total or partial, phospholipase A2 enzyme activity. This patent presents therapeutical pharmaceutical formulations containing anti-serum to snake and/or insect venoms wherein the anti-serum has been preferably affinity purified for use in treating patients suffering from neoplastic disease. This patent presents pharmaceutical formulations containing organic polymer mimic molecules generated to snake and/or insect venoms, and/or Pospholipase C enzyme preparation or extract from such venoms which may contain, total or partial, phospholipase A2 enzyme activity or activities similar to other neuro-active peptides.

In this patent the affinity purified anti-serum to venoms are shown to be active anti-proliferative neoplastic agents.

The present invention comprises the method of treating host organisms (ie human or animal) in need of a drug having anti-neoplastic activity comprising the administration of a therapeutically effective amount of venom anti-serum either alone or preferably in combination with a Phospholipase C inhibitor of non-toxic nature or monoclonal or polyclonal anti-serum to Phsopholipase C enzyme or a vaccine containing in whole or in part venom and other components showing Phospholipase A_2 and/or Phospholipase C activity. This patent presents pharmaceutical formulations containing snake and/or insect venoms, or extracts from such venoms which may contain, total or partial, Phospholipase A_2 enzyme activity alone or in combination with Phospholipase C inhibiting compounds or Phospholipase C mono or polyclonal anti-serum to Phospholipase C enzyme as therapeutic vaccine candidate for all neoplastic diseases. This patent presents therapeutic pharmaceutical formulations containing anti-serum to snake and/or insect venoms wherein the anti-serum is preferably affinity purified

for use in treating neoplastic diseases. This patent presents pharmaceutical formulations containing organic polymer mimic molecules generated to snake and/or insect venoms, or extract from such venoms or synthetic peptides or other molecules which may contain, total or partial, Phospholipase A_2 and C enzyme activity.

Affinity purified anti-serum to venoms are shown herein below, by way of example, to be active in-vitro and in-vivo anti-proliferative neoplastic agents. Accordingly, these affinity purified antisera either alone but preferably in combination with non-toxic Phospholipase C inhibitor or anti-serum to Phospholipase C are useful in the control of proliferation of neoplastic tissue.

BACKGROUND OF THE INVENTION

There is evidence to indicate that Phospholipase A2 (PLA_2) is involved in the pathogenesis of many diseases. Thus local and circulating levels of Phospholipase A_2 enzyme and enzymatic products are elevated during infection, inflammatory diseases, tissue injury and brain dysfunction and is a very early indication of neoplastic development prior to tumour

cell mass being evident by conventional methods of scanning tissue tumours.

Excessive Phospholipase A_2 activity may promote chronic inflammation, allergic reaction, tissue damage and pathophysiological complications. These effects may be the result of accumulating Phospholipase A_2 products (lysophospholipids and free fatty acids, e.g. Arachidonic Acid) and destruction of key structural phospholipid membrane components, but are potentiated by secondary metabolites, such as eicosanoids and platelet-activating factor. Phospholipase A_2 products or lipid mediators derived there from have been implicated in numerous activities that are an integral part of cell activation; chemotaxis, adhesion, degranulation, phagocytosis and aggregation.

Phospholipase A_2 secreted excessively at local sites may be responsible for tissue damage common to rheumatic disorders, alveolar epithelial injury of lung disease and reperfusion.

During acute myocardial ischemia, cytosolic Phospholipase A_2 and Phospholipase C activation causes increased intracellular Ca^{2+}. Subsequent accumulation

of lysophospholipids and free fatty acids promote damage to sarcolemmal membranes leading to irreversible cell injury and eventually cell death.

Altered cytosolic Phospholipase A_2 and Phospholipase C activity or defects in their control and regulation is a predisposing factor to causing tumour cell development.

Prostaglandins and related eicosanoids are important mediators and regulators of both immune and inflammatory responses. Prostaglandin E_2 induces bone resorption and Leukotriene B_4 stimulates vascodilation and chemotaxis. Increased levels of Phospholipase A_2 is noted in Rheumatoid Arthritis (R.A.), osteoarthritis and gout, collagen and vascular diseases. Phospholipase A_2 induces non specific airway hyperactivity that is evident in asthma. Phospholipase A_2 is also elevated in peritonitis, septic shock, renal failure and pancreatis.

The activity of cell-mediated defense systems is stimulated by consecutive formation of interleukin -1ß (IL-1ß), interleukin-2 (IL-2) and interferon γ (IFN γ). The system is inhibited by interleukin-4 (IL-4) and

also by prostaglandin E_2 (PGE_2) and histamine, which are released when the immune system is activated. The inhibition is strong in cancer patients, because PGE_2 is formed in many cancer cells and its formation is stimulated by IL-1B. PGE_2 and histamine are feedback inhibitiors of cell mediated immunity.

PGE_2 is formed from arachidonic acid in monocytes, macrophages, cancer cells and other cells, when arachidonic acid is released from cellular phospholipids. The formation of PGE_2 is stimulated by several compounds, including histamine, IL-1 (α and β) and Tumour Necrosis Factor α (TNFα). PGE_2 inhibits the formation and receptor expression of IL-2 by increasing the level of cyclic AMP (cAMP) in helper T cells. This concomitantly decreases the formation of IFN γ.

PGE_2 inhibits the ability of natural killer cells (NK) to bind with tumour cells by increasing cAMP in Natural Killer cells. This decreases tumour cell killing.

When the immune system is stimulated to destroy tumour cells, the killing is prevented because IL-1B stimulates PGE_2 formation in tumour cells, which

increases cAMP levels in NK cells and prevents the binding of NK and tumour cells.

The activation of the cell-mediated defense is blocked also because PGE_2 increases cAMP in helper T cells and inhibits the formation of IL-2 and INF γ.

Cytotoxic T cells can also produce PGE_2 thus inhibiting the activity of NK cells.

A number of human and experimental animal tumours contain and/or produce large quantities of prostaglandins (PG). Prostaglandins E_2 has been shown to effect significantly cell proliferation in tumour growth and to suppress immune responsiveness.

Inositol phospholipid - specific phospholipase C (PLC) is involved in several signaling pathways leading to cellular growth and differentiation.

Phosphatidylinositol specific phospholipase C is an important enzyme for intracellular signalling. There are at least three major classes of Phosphatiylinsitol specific Phospholipase C PtdInsPLC: PtdInsPLC β, γ, δ. PtdInsPLCs hydrolyse a minor

membrane phospholipid, phosphatidylinositol (4,5) bisphosphate (PtdIns (4,5) P_2) to give the second messengers inositol (1, 4, 5) trisphosphate (Ins (1, 4, 5) P_3), which releases Ca^{++} from intracellular stores to increase the intracellular free Ca^{++} concentration, and diacylglycerol which activates the Ca^{++} and phospholipid-dependent protein serine/threonine kinase, protein kinase C. Proteins phosphorylated by protein kinase C include transcription factors. Together, the increase in intracellular free Ca^{++} concentration and the activation of protein kinase C lead to a series of events that culminate in DNA synthesis and cell proliferation in tumour cells.

A number of growth factors and mitogens, including platelet-derived growth factor (PDGF), epidermal growth factor (EGF) and bombesin, act through specific receptors to increase Ptd Ins PLC activity in cells. Continued stimulation of Ptd Ins PLC can lead to cell transformation.

Ptd Ins PLC activity is found to be increased in a number of human tumours. 76% of human breast cancers have detectable Ptd Ins PLC-γ immunoreactive protein compared to only 6% in benign breast tissue.

Cytosolic Ptd Ins PLC activity is increased up to >4-fold in human non-small cell lung cancer and renal cell cancer compared to normal tissue.

SUMMARY OF THE INVENTION

The present invention comprises the method of treating mammals including humans in need of a drug to prevent neoplastic tissue growth and spread by the administration of a therapeutically effective amount of venom anti-serum prepared to whole venom or to parts of the venom or its components related to activating Phospholipase A_2. Also enhanced anti-cancer effects both in-vitro and in-vivo have been realised by combining this affinity purified antiserum to venoms with a non-toxic inhibitor of Phospholipase C or with anti-serum (polyclonal or monoclonal) developed to Phospholipase C enzyme.

This patent relates to the administration of one or more compounds which can generally be described as performing their function by either directly or indirectly causing Phospholipase A2 and Phospholipase C enzyme inhibition, wherein the said inhibition is either partial or total. In addition this patent relates to the administration of one or more compounds

which can generally be described as performing their function by interaction with the neoplastic cells causing them to alter their metabolism and thereby preventing their growth or spread, thus preventing further disruption of non-involved organs of the body and causing no toxicity to the infected patient or animal being treated.

Additional aspects of the invention relates to pharmaceutical compositions containing the compounds of the invention as active ingredients, modifying unwanted immune responses, and to methods of retarding proliferation of tumour cells using the compounds and compositions of this invention.

The anti-serum to venoms are shown herein to be active anti-tumour proliferative compounds and immune enhancing. For use in this regard, the compounds of the invention are administered to mammals, including humans, in an effective amount of 0.05 to 5 gms per day per kilogram of body weight. The amount depends, of course, on the condition to be treated, the severity of the condition, the route of administration of the drug, and the nature of the subject. The drugs may be administered IV, orally, parenterally, or by other

standard administration routes.

The therapeutic activity of the compounds of this invention are demonstrated by inhibition of the tumour cell lines in-vitro and in-vivo. The compound was tested for toxicity in Scid mice. Results as in Figure A1.

Toxicity Study

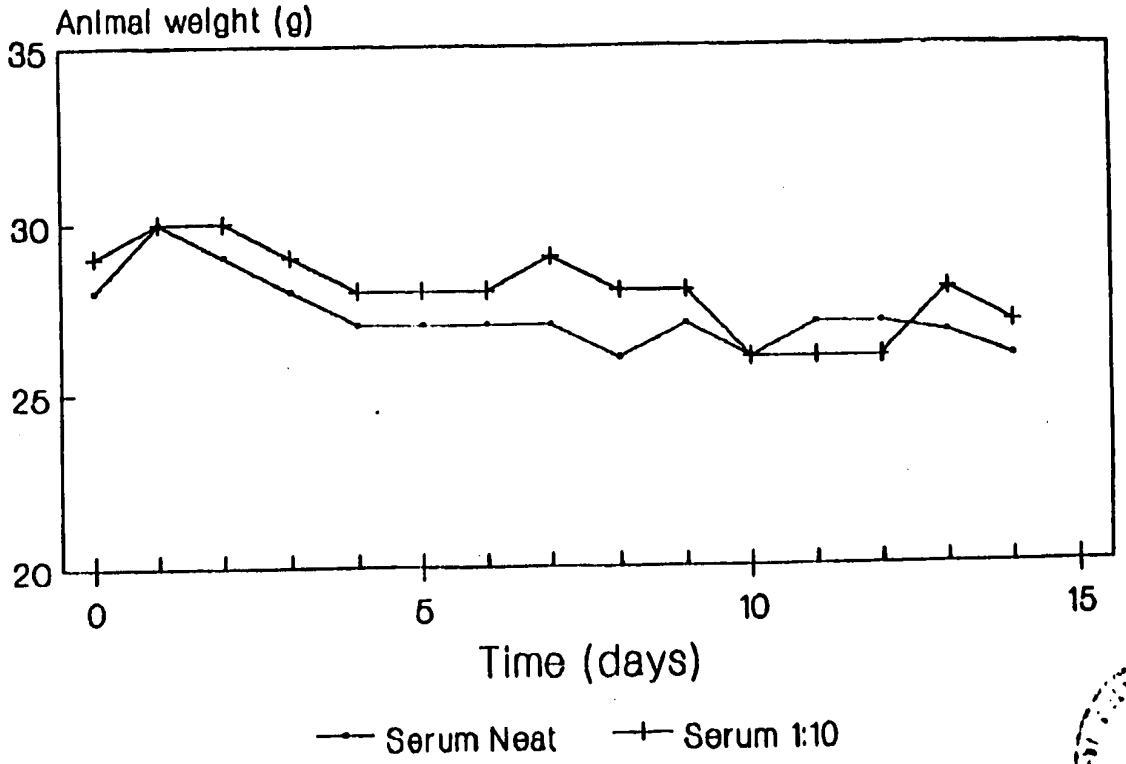
Method

Female Scid mice (6-8 weeks of age) were treatedwith either a Neat or a 1:10 dilution of the serum preparation, subcutaneously (0.1ml, daily) for a period of 14 days. The weights of the mice were measured daily. At termination, organs were removed and fixed in formal calcium for histological examination.

Results

No toxicity, as assessed by animal weights and clinical well-being, was evident (Figure A1).

Figure A1
Toxicity Data



The compounds of this invention may be combined with other known anti-inflammatory/immunosuppressive agents such as steroids or non-steroidal anti-inflammatory agents (NSAID) in the pharmaceutical compositions and methods described herein.

Anti-serum to snake and/or insect venoms can be used as a therapeutic treatment in diseases where elevated levels of Phospholipase A_2 are evident, (eg Rheumatoid Arthritis, see Fig. B). It is also envisaged that this novel therapy with anti-serum to venoms (snake or insect) can be applied as a prophylactic therapy by using sub-lethal doses of venoms or the venom enzyme extracts together with adjuvant to stimulate an immunoglobulin response within the patient. It is also envisaged that a synthetic peptide incorporating the Phospholipase A_2 and/or Phospholipase C activity could be used to generate said anti-serum as vaccine or therapeutic agent. Use may also be made in the generating of this therapeutic vaccine/anti-serum by using the known sequence homology that exists between human Phospholipase A_2 and snake/insect venoms used in combination with compounds known to inhibit Phospholipase C activity or anti-serum developed to this enzyme.

An extracellular inhibitor of Phospholipase A_2 which effects the enzyme at the cell membrane surface but does not penetrate into the cell cytoplasm may be very desirable and this is achieved by the use of carrier moieties. Attached to the antibodies the primary role of the carrier moiety is to increase the size (molecular volume) of a Phospholipase A_2 inhibitor forming the Phospholipase A_2-inhibitor moiety of the composition of this invention sufficient to render the latter cell-impermeable.

The compounds of this invention possess the valuable pharmacological properties of the Phospholipase A_2 and Phospholipase C inhibitor moiety thereof but lack the side effects associated with cell penetration.

Sustained or directed release compositions can be formulated, e.g. liposomes or those wherein the active compound is protected with differtially degradable coatings, e.g. by microencapsulation, multiple coatings, etc.. It is also possible to freeze-dry the new compounds and use the lyophilizates obtained, for example, for the preparation of products for storage and subsequent injection.

EXPERIMENTATION

The compounds of this invention can be identified as anti-serum to venoms or Phospholipase C or mimic molecules generated to venoms or Phospholipase C or parts thereof also the pharmaceutical use of venoms or enzyme components as vaccine antigen are incorporated. Non-toxic compounds showing anti-phospholipase C activity can be incorporated with the anti-serum to venoms, or mimic molecules demonstrating Phospholipase A_2 activity.

In certain applications of this therapy it will be necessary to curtail the ADCC reaction which could cause serum sickness and to ensure that this does not occur the IgG (FC) component is enzymatically cleaved from the affinity purified immunoglobulin so that natural killer T cells will not react to the anti venom immunoglobulin in the anti-serum.

Ability of anti-serum to snake venom to inhibit Phospholipase A_2 enzyme isolated from human synovial fluid (Figure A2).

The inhibition of Phospholipase A2 enzyme from synovial fluid isolated from a patient with Rheumatoid

Arthritis was tested with a range of dilutions of anti-serum to snake venom. Anti-serum to snake venom generated in horse, reconstituted in 10ml sterile water. The following dilutions were used 1:10, 1:20, 1:40 and 1:60. The method used was as outlined in "Infection and Immunity, Sept. 1992, p. 3928-3931. Induction of Circulating Group II Phospholipase A2 Expression in Adults with Malaria.

Results (Figure A2)

Dilution	Inhibition
1:10	63%
1:20	50%
1:40	35%
1:60	29%

In-vitro testing of un-affinity purified snake venom.

A range of tumour cell lines were tested with 3 concentrations of the anti-serum to snake venom by the MTT Assay. This anti-serum was not affinity purified. MTT Assay described by Alley et al, (Cancer Research, 48: 589 - 601, 1988) See Figure B.

SUMMARY OF RESULTS (Figure B)

Molt 4: Human T Cell Lymphoma Cancer

Serum-containing	
Dilution	*% of Control*
Neat	*48.1*
1:10	*53.7*
1:20	*40.8*
Serum-Free	
Neat	*58.7*
1:10	*51.2*
1:20	*40.6*

MDA 468: Human Breast Cancer

Serum-containing	
Dilution	*% of Control*
Neat	*8.0*
1:10	*53.7*
1:20	*58.9*
Serum-Free	
Neat	*15.4*
1:10	*48.4*
1:20	*58.9*

C170HM2: Human Colon Cancer

Serum-containing	
Dilution	% of Control
Neat	9.3
1:10	61.4
1:20	55.6
Serum-Free	
Neat	15.2
1:10	47.3
1:20	49.5

Pan 1: Human Pancreatic Cancer

Serum-containing	
Dilution	% of Control
Neat	9.3
1:10	47.5
1:20	49.2
Serum-Free	
Neat	43.1
1:10	53.2
1:20	69.4

841: Human small cell lung cancer

Serum-containing	
Dilution	% of Control
Neat	25.2
1:10	45.5
1:20	51.1
Serum-Free	
Neat	63.4
1:10	60.1
1:20	59.8

T24: Human Bladder Cancer

Serum-containing	
Dilution	% of Control
Neat	63.5
1:10	75.1
1:20	76.2
Serum-Free	
Neat	84.1
1:10	87.9
1:20	83.4

Testing un-affinity purified anti-serum to Snake Venom against B16 F1 Melanoma Cell line.

Mice

C57BL/6

Procedure

The mice were inoculated with 0.5×10^6 B16 F1 melanoma cells subcutaneously (sc) into flank region. Once palpable tumours had developed the mice received daily sc injections as follows:-

			number of mice
A	-	sterile water 100ul	6
B	-	anti-serum (full strength) 100ul	6
C	-	anti-serum (diluted 1:10) 100ul	6

The dimensions of the tumours were taken daily using callipers. Once the tumours of the control mice were approximately 1.5cm or larger in diameter all mice were killed. The tumours were removed and weighed.

Results

Small tumours were first discernible by palpitation in all mice 6-7 days after inoculation.

The changes in volume as measured by callipers, together with tumour weights at autopsy. See Fig. C for effect of anti-serum to snake venom on tumour growth retardation.

Effect of un-affinity purified anti-serum to snake venom on Melanoma B16F1 Growth

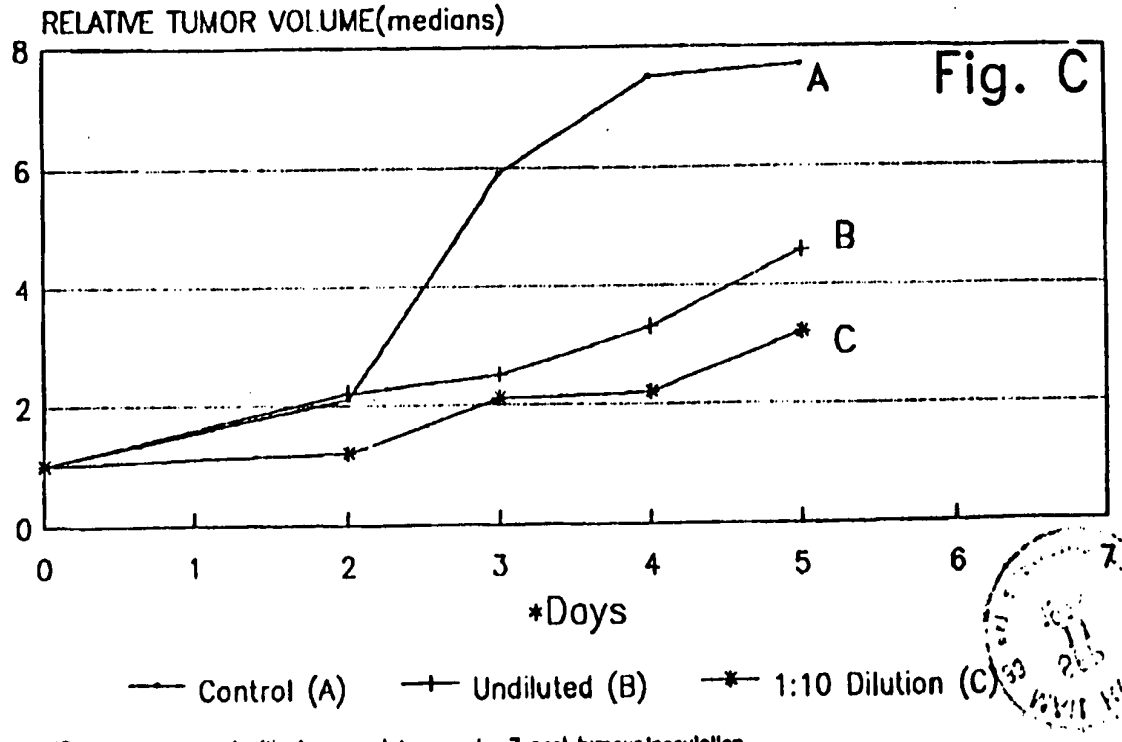


Fig. C

*Days are measured with day zero taken as day 7 post tumour inoculation.

IN VITRO SCREENING OF THE AFFINITY PURIFIED ANTI-SERUM TO SNAKE VENOM PREPARATION AGAINST A RANGE OF TUMOUR CELL LINES (Illustrated in Fig. D)

Introduction

The in vitro inhibitory effects of the horse generated anti-serum to snake venom preparation, previously evaluated were obscured due to serum enhancement of tumour cell growth. Thus in the following assay, affinity purified anti-serum to snake venom was evaluated.

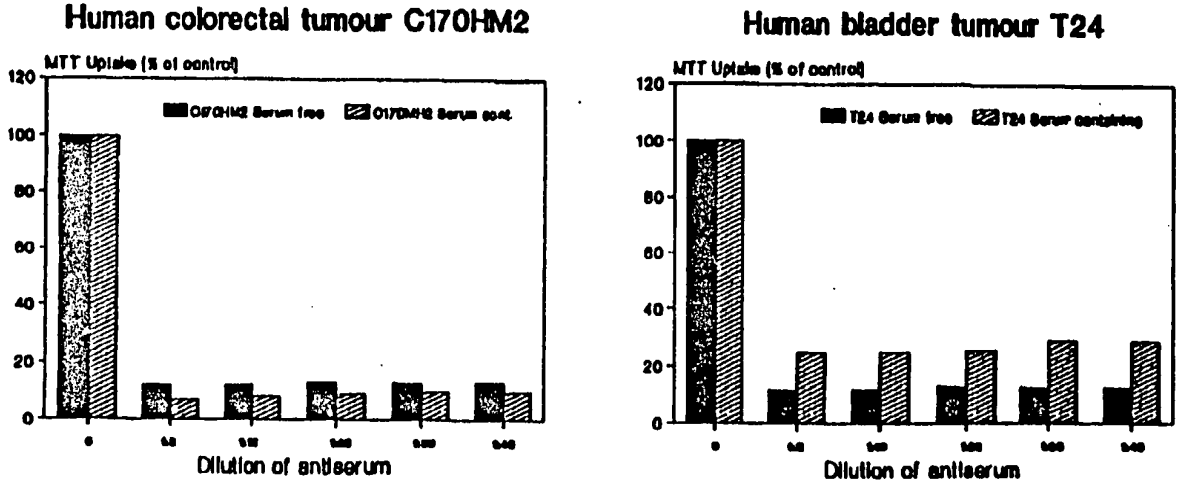
Method

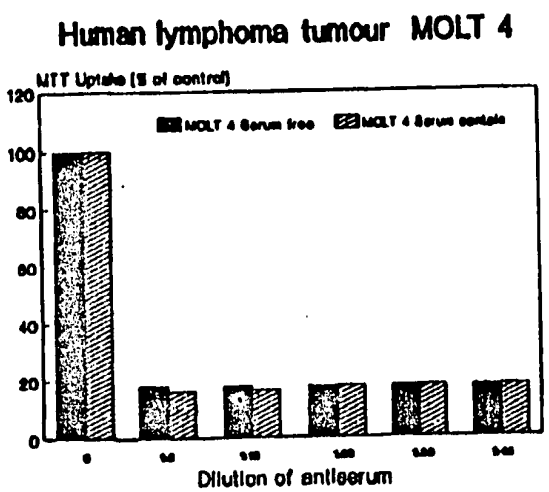
The cell lines were seeded into 96 well plates at a cell concentration of 1e4 cells per well in both serum free (Hams F12:RPMI 1640 + 0.5% bovine serum albumen) and serum-containing medium (RPMI 1640 + 10% heat inactivated foetal calf serum). The antiserum preparation was diluted in the corresponding medium and added to the wells, 2-3 hours after the cells (to allow for cell adherance). The plates were incubated at 37°C in 5% CO_2 for 3 days. The cells were then incubated with 1 mg/ml MTT (methyl thiazol tetrazolium) for 4 hours at 37°C. The crystals were then solublised with dimethyl sulphoxide and the absorbance measured at 550nm.

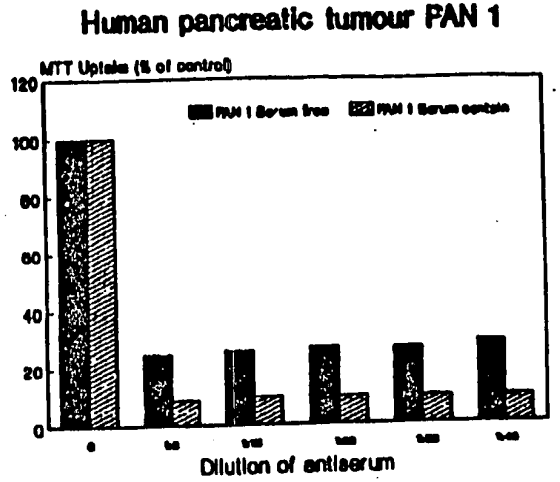
Results

The test anti-sera inhibited all of the cell lines at all concentrations examined. The level of inhibition was statistically significant from the untreated control at all antiserum dilutions, with all cell lines as assessed by a one way analysis of variance.

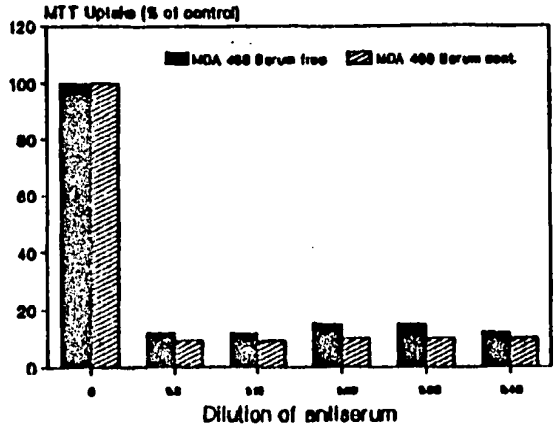
Figure D



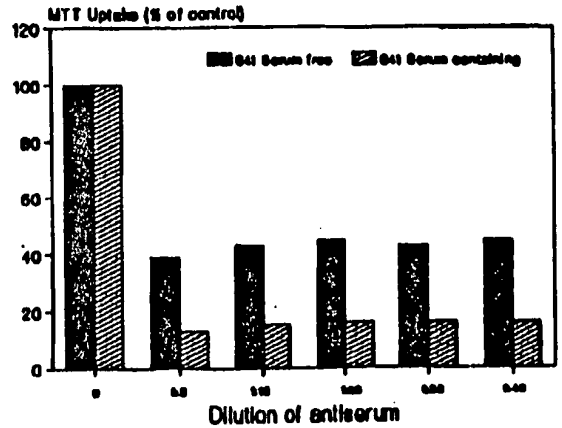

Human lymphoma tumour MOLT 4
MTT Uptake (% of control)
120
100
80
60
40
20
0
MOLT 4 Serum free
MOLT 4 Serum contain
Dilution of antiserum

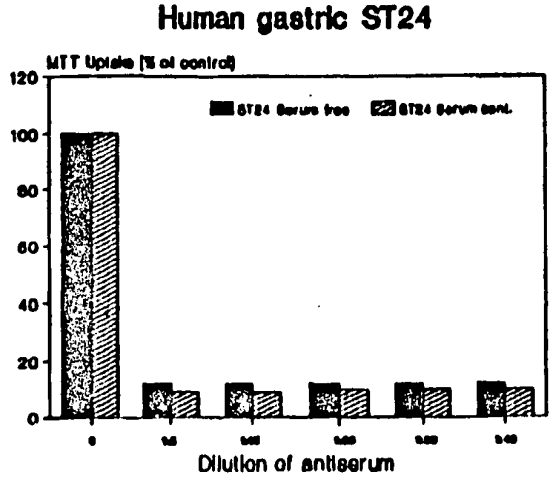

Human pancreatic tumour PAN 1
MTT Uptake (% of control)
120
100
80
60
40
20
0
PAN 1 Serum free
PAN 1 Serum contain
Dilution of antiserum

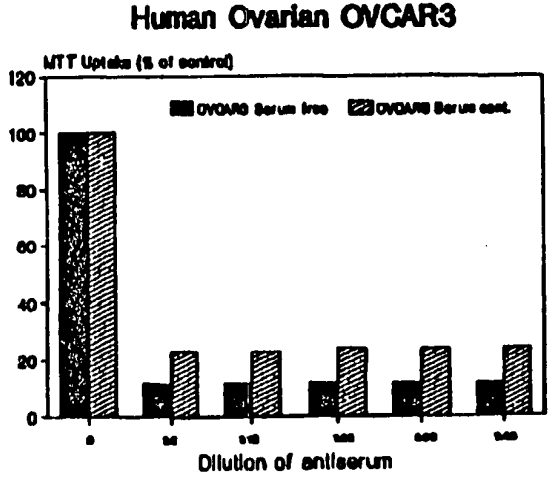
Human breast tumour MDA 468



Human small cell lung tumour 841




Human gastric ST24
MTT Uptake (% of control)
120
100
80
60
40
20
0
Dilution of antiserum


Human Ovarian OVCAR3
MTT Uptake (% of control)
120
100
80
60
40
20
0
Dilution of antiserum

28

IN-VIVO TEST

The effects of affinity purified anti-serum to snake venom on human colorectal C170HM₂ cell line.

Materials and Methods

C170MH2 cells were injected subcutaneously into the left flank of ten male nude mice. The mice were allocated randomly to two groups.

Group 1 - 100µl anti-serum twice daily intravenously (IV)

Group 2 - 100µl PBS twice daily IV

Tumours were measured twice weekly, using callipers, in two dimensions. Cross-sectional areas were calculated. The mice were also weighed once weekly. The therapy was terminated at day 22.

Results

The cross-sectional areas were measured at increasing time points during the experiment, as shown in Fig. E. The afinity purified anti-serum preparation induced a slowing in growth when compared to saline controls. An ANOVA was performed on the results in which the treatment was evaluated with respect to time,

and shows a significance of P = 0.028.

At the termination of the experiment, the tumours were weighed and the results are shown in Fig. F. No toxic effect of the affinity purifed anti-serum preparation was observed.

Figure E: Effect of affinity purified anti-serum to snake venom on the mean cross-sectional area of C170HM2 in nude mice

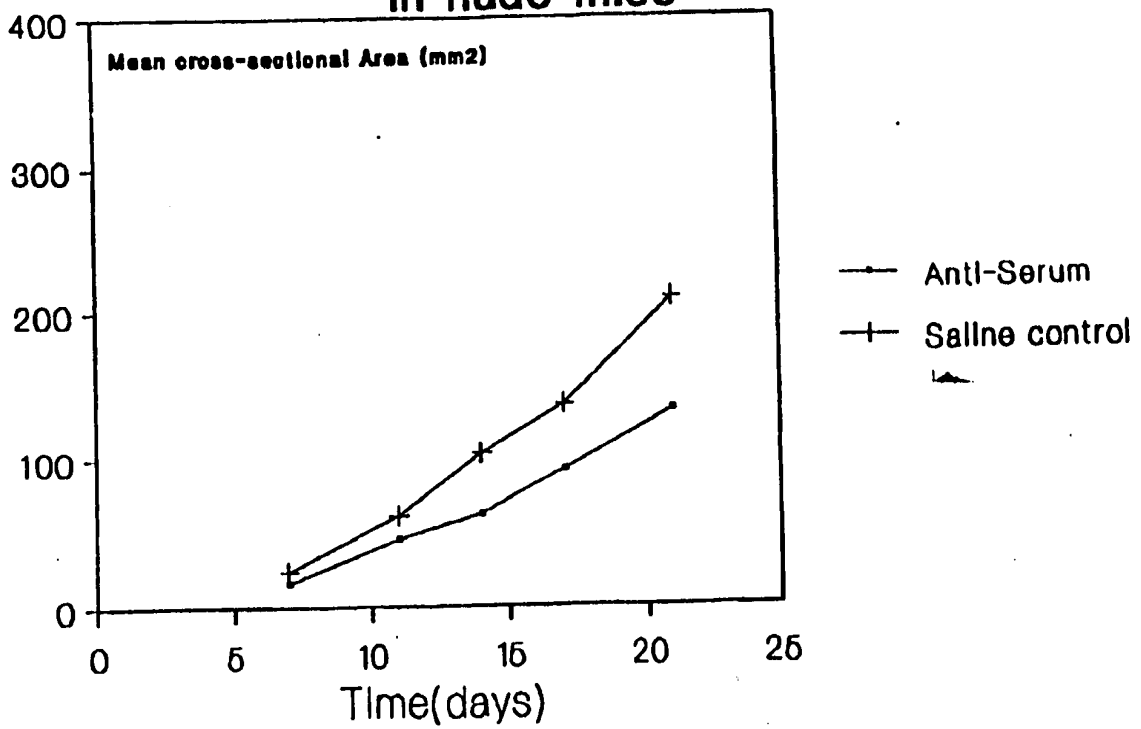
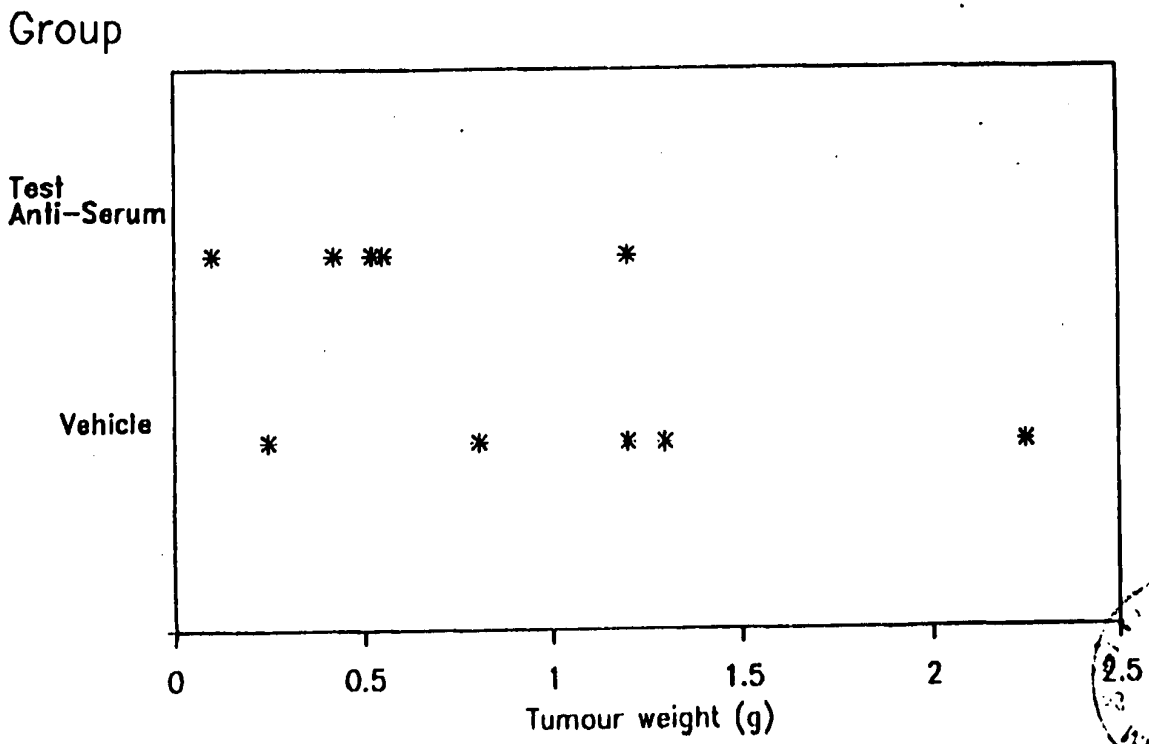


Figure F: Effect of affinity purified anti-serum to snake venom on the final tumour weight of C170HM2



In-vitro screen of the affinity purified anti-serum to snake venom preparation in combination with a phospholipase C inhibitor 1-oleoyl-2-acetyl-sn-glycerol (OAG) 5μ molar, on a range of cancer cell lines.

Methods.

The affinity purified anti-serum to snake venom preparation was diluted 1:2 and 1:10 and was combined with 5μ molar OAG and added to the wells as previously described for the MTT assay. The cell lines tested were Human Breast tumour, MDA 468, Human small cell lung tumour 841 and Human renal TK-10. Results as shown in Fig. G.

Figure G: Affinity purified anti-serum to snake venom and (OAG) a Phospholipase-C inhibitor combination.

Human breast tumour MDA 468

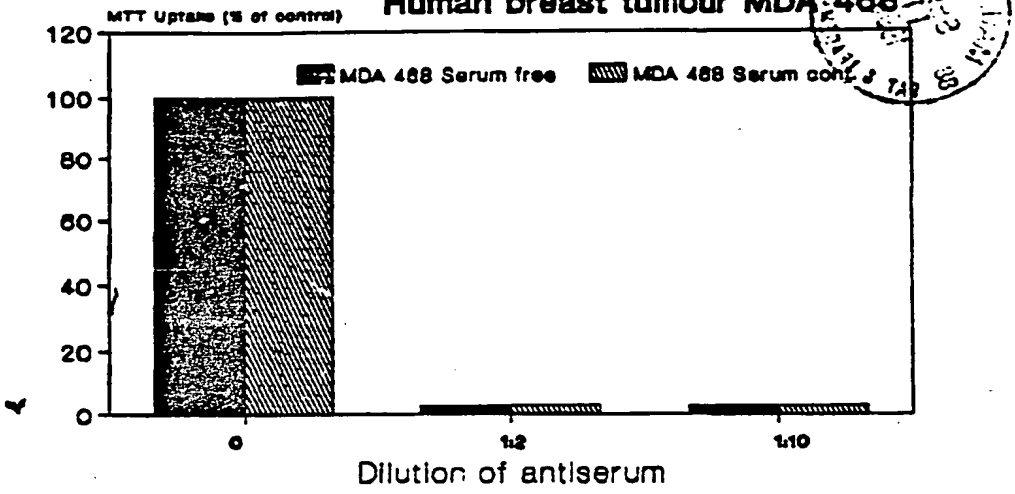


Figure G: Affinity purified anti-serum to snake venom and (OAG) a phospholipase C inhibitor combination

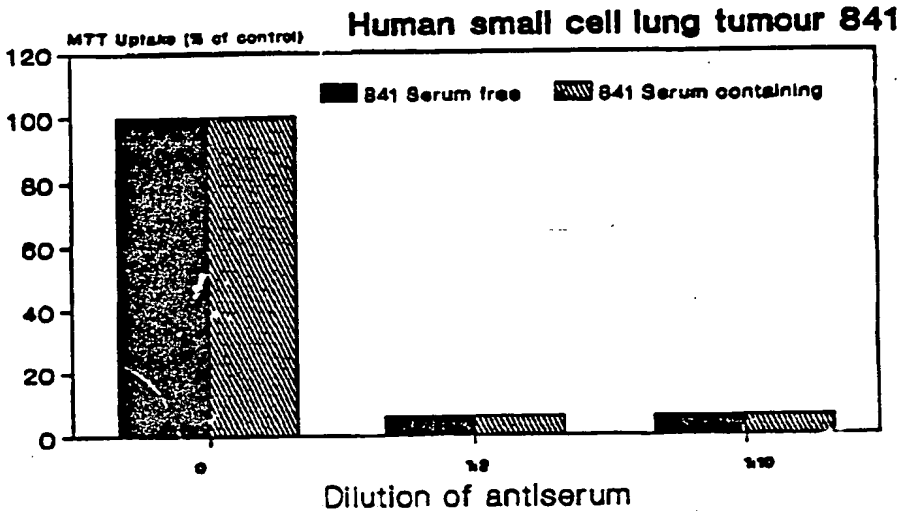
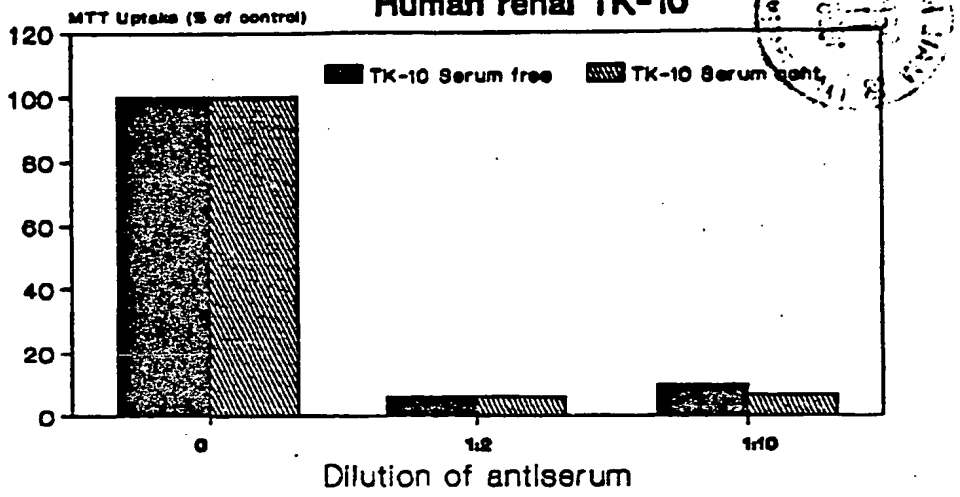


Figure G: Affinity purified anti-serum to snake venom and (OAG) a phospholipase C inhibitor combination

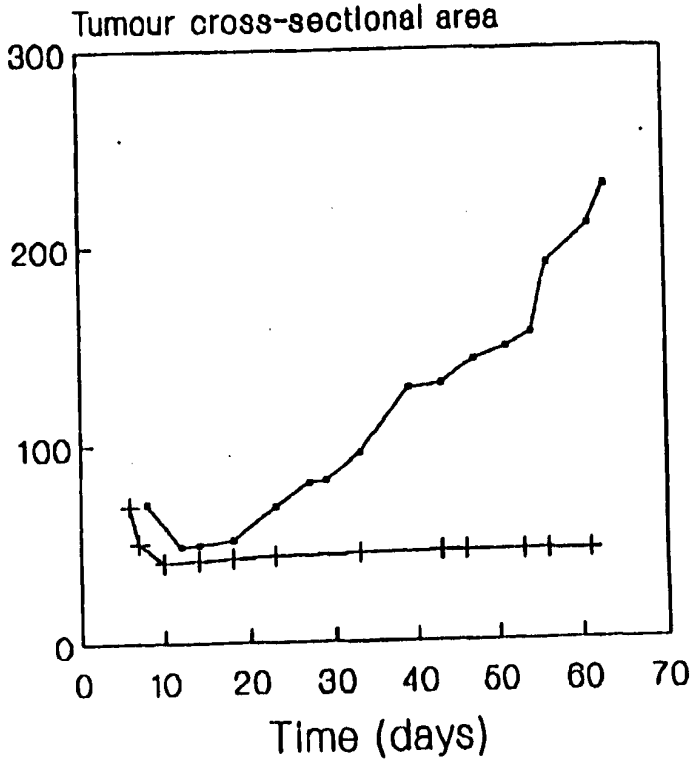


In-vivo testing of the combination of affinity purified anti-serum to snake venom and 1-oleoyl-2-acetyl-sn-glyceral (OAG) at 5µm concentration on the growth of MDA 468 cell line.

Method

MDA 468 tumours were aseptically removed from donor female Scid mice. The tissue was aseptically minced, pooled and implanted into anaesthetised female Scid mice (anaesthetic comprised of a 0.2ml injection of Hypnorm (Jannsen):Hypnovel (Roche):distilled water in a 1:1:5 ratio). Tissue implants consisted of 3-5 mm² pieces and after subcutaneous transplantation into the left flank, the incision was clipped. The Scid mice were then randomised into 2 groups of 10 animals. They were treated daily with a 0.2ml subcutaneous injection (in the opposite flank to the tumour graft) of a combination of affinity purifed anti-serum to snake venom and 5µm molar of (OAG) dilution of the anti-serum preparation. The control animals received 0.2ml phosphate buffered salinc, pH 7.6. All animals were terminated on day 63, and the tumours were dissected out, weighed and processed for histology. Results are in Fig. H.

Figure H:Effect of the affinity purified anti-serum to venom in combination with the Phospholipase C inhibitor (OAG) 5µm



Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilise the present invention to its fullest extcnt. The preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the disclosure in any way whatsoever.

I Claim

1. A method of treating neoplasm in mammals by the administration of a therapeutic agent containing venom anti-serum reactive with Phospholipase A2 enzyme causing inhibition of same or anti-serum polyclonal or monoclonal directed to any component of the venom preparation demonstrating Phospholipase A2 activity.

2. A method of treating mammals prophylactically to prevent neoplastic development by the administration of a therapeutic vaccine containing venom or part thereof as the principal antigen component.

3. Pharmaceutical formulations containing venom anti-serum or part thereof in combination with anti-serum to Phospholipase C enzyme or part thereof or inhibitory compounds to Phospholipase C for use as a therapeutic agent for the therapy of any neoplastic condition in a human or animal.

4. Pharmaceutical formulations containing one or more venoms or venom components as antigen in combination with Phospholipase C enzyme or enzyme components of animal or plant origin also as antigen components for the generation of a prophylactic vaccine therapy whose

immune response in animals or human would confer protection from tumour cell development.

5. A method according to Claims 2, 3 or 4 wherein the venoms used may contain total or partial phospholipase A2 enzyme activity.

6. A method according to Claim 5 wherein a phospholipase enzyme C inhibitor is used in combination with the venom anti-serum of Claim 1 to enhance anti neoplastic and anti metastatic activity.

7. A method according to Claims 1, 2, 3 or 4 wherein the administration is part of a combination therapy with other therapeutically effective agents, such as that specified in Claim 6.

8. A method according to Claims 2,3 or 4 wherein the administration is in combination with adjuvants.

9. A method according to Claims 1,2,3 or 4 wherein the venom is that of snake and/or insect.

10. A method according to Claims 1,2,3 or 4 wherein the venom showing Phospholipase A_2 activity is

obtained from more than one species of snake and/or insect.

11. A method according to Claims 1 and 3 wherein the therapeutic anti-serum is either totally or partially affinity purified.

12. A method according to Claims 1 to 11 wherein the therapeutic agent is administered as an anti-inflammatory agent.

13. A method according to Claims 1 to 11 wherein the therapeutic agent is administered as an inhibitor of nerve growth factor.

14. A method according to Claims 1 to 11 wherein the therapeutic agent is administered as an inhibitor of lipooxygenase.

15. A method according to Claims 1 to 11 wherein the therapeutic agent is administered as an inhibition of cyclooxygenase product synthesis.

16. A method according to Claims 2 and 4 wherein the therapeutic agent is administered as adjuvant therapy

associated with organ and tissue transplants.

17. A method according to Claims 1 and 3 wherein the therapeutic agent is administered to prevent the occurrence of immunosuppressant.

18. A method according to Claims 1 and 3 wherein the therapeutic agent is administered in the treating of allergic contact dermatitis, Asthma and Psoriasis.

19. A method according to Claims 1 and 3 wherein the therapeutic agent is administered as an anti-proliferative agent either alone or specifically cell targeted.

20. A method according to Claims 1 and 3 wherein the anti-serum is administered for the treatment of physiological conditions resultant from elevated levels of phospholipase A2 products or metabolites and/or Prostaglandin E2.

21. A method according to Claims 1 to 4 wherein the anti-serum to Phospholipase A_2 and C are produced by molecular imprinting from template molecules generated from organic polymer mimic molecules of these enzymes.

22. A method according to Claims 1,2,3 or 4 wherein the therapeutic agent contains a carrier moiety to increase molecular size and restrict cell penetration.

23. Therapeutic agents according to Claims 1,2,3 or 4 for treating one or more of the following:- rheumatoid arthritis, osteoarthritis, gout, rheumatic carditis and autoimmune diseases such as allergic diseases, bronchial asthma, septic shock, renal failure, pancreatis, myasthenia gravis and ocular and dermal inflammatory diseases, psoriasis, neoplasis, splenomegaly, cancer, metastatic spread of neoplasm, collagen vascular disease, myocardial ischemia, cellular chemotaxis, depression, erythema, vascular permeability resultant from enhanced production of PGE_2, acne, atopic diseases, malaria, allergic conjunctivitis, schizophrenia, reiters syndrome, raynaud's phenomenon, lupus.

24. A method according to Claims 1 and 3 wherein the Fc receptor of the antibody to either Phospholipase A_2 and C used in this therapeutic method is either totally or partially removed.

25. A method according to Claim 7 wherin the combination therapy is chemotherapy and/or radiotherapy.

26. A method according to Claims 1 and 3 wherein the the therapy contains mono and/or poly clonals to venoms.

27. A method according to Claims 1 and 6 wherein a non-toxic compound demonstrating inhibiting activity against Phospholipase C enzymes may be utilised in conjunction with the venom anti-serum to enhance its anti-neoplastic (tumour) and anti-metastatic activity.

28. A method according to Claims 1 and 3 wherein the anti-serum is generated to human Phosphoslipase A2 enzyme either in a mono and/or poly clonal form.

29. A method according to Claims 1 and 3 wherein the anti-serum to venom Phospholipase A2 is generated in eggs, this method produces antibodies which do not react with the human Compliment system but which effectively enhance immune function and cause cell death to cancer and/or tumour cells.

30. A method according to Claims 1 and 3 wherein the anti-serum to venom Phospholipase A2 is generated in mammals and extracted from the colostrum and preferably but not essentially affinity purified for use in oral administration to patients either alone or in combination with antiserum similiarly produced to human Phospholipase C enzyme components.